**Nos. 2022-2217, 2023-1021**

# UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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**UNITED THERAPEUTICS CORPORATION,**
*Plaintiff-Cross-Appellant,*

**v.**

**LIQUIDIA TECHNOLOGIES, INC.,**
*Defendant-Appellant.*

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On Appeal from a Judgment of the United States District Court for the District of Delaware, No. 20-cv-755 (Andrews, J.)

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## CROSS-APPELLANT'S REPLY BRIEF

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## GLOSSARY

| | |
|---|---|
| ’066 Patent | U.S. Patent No. 9,593,066 |
| ’393 Patent | U.S. Patent No. 8,497,393 |
| DMF | Drug Master File |
| LIQ861 | bulk inhalation powder that Liquidia processes from treprostinil sodium |
| Liquidia | Defendant-Appellant Liquidia Technologies, Inc. |
| Liquidia Response Br. | Corrected Defendant-Appellant’s Response and Reply Brief, ECF No. 32 |
| Moriarty 2004 | Moriarty et al., *The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15*, 69 J. Org. Chem. 1890-1902 (2004) (Appx1471-1483) |
| NDA | new drug application |
| POSA | person of ordinary skill in the art |
| PRINT | Particle Replication in Nonwetting Templates |
| PTAB | Patent Trial and Appeal Board |
| PTO | U.S. Patent and Trademark Office |
| TN | treprostinil sodium |
| UTC | Plaintiff-Cross-Appellant United Therapeutics Corporation |
| UTC Br. | Cross-Appellant’s Corrected Principal and Response Brief, ECF No. 35 |

## INTRODUCTION

As UTC's principal brief explained, the district court made numerous legal errors in evaluating infringement and anticipation of the '066 Patent. Rather than address those errors head on, Liquidia's reply attempts to make new factual findings to justify the district court's flawed conclusions.

On infringement of the ambient-storage limitation, Liquidia barely defends the district court's holding that UTC needed to demonstrate past infringement. For good reason. In this pre-launch Hatch-Waxman case, the infringement inquiry focuses on the scope of Liquidia's NDA. *See Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1279 (Fed. Cir. 2013). And Liquidia's NDA seeks permission to market an infringing product: it touts stability at ambient temperature, relies on "representative" batches that were stored at ambient temperature, and incorporates a specification that imposes no storage-temperature requirement. Resisting this conclusion, Liquidia argues that treprostinil salt is "never" stored outside of the 2-8°C range recommended by Yonsung's treprostinil-salt label. But the district court did not buy this argument, and rightly so: as the court noted, Liquidia accepted numerous

batches that were stored outside of this range or whose temperature was not monitored at all. Liquidia's argument also misses the point: what matters is the scope of the NDA, and Liquidia's NDA contains no enforceable requirement to maintain a storage temperature of 2-8°C during manufacturing and shipment.

Liquidia offers more of the same regarding the other infringement issues. It invents a finding that treprostinil sodium was being *actively used* in a drybox, rather than defend the district court's conclusion that storage during the manufacturing process cannot constitute storage within the meaning of the claims. It similarly tries to defend the district court's disregard of storage that occurred between steps of the PRINT process by offering a new construction of "pharmaceutical composition" and "pharmaceutical product" that the district court expressly rejected, and a new finding (belied by Liquidia's own labeling) that any treprostinil sodium was fully dissolved at the beginning of the PRINT process. This reimagining of the district court's factfinding cannot sustain the district court's legally indefensible conclusion.

On anticipation of UTC's product-by-process claims, Liquidia advances two arguments that are directly contrary to circuit precedent.

First, Liquidia argues that this Court should ignore the structural benefits conferred by the claims—the reduction (as compared to the prior art) of impurities generated by alkylation and hydrolysis—because those specific impurities are not expressly recited in the claims. *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340 (Fed. Cir. 2009), forecloses this argument. Second, with the claims properly construed to account for the structural benefits, Liquidia provided no evidence that its sole prior-art reference (Moriarty 2004) disclosed the claimed invention. So it attempts to shift the burden to UTC to *dis*prove anticipation—another argument *Amgen* rejected.

This Court should reverse the district court's conclusions regarding infringement and anticipation.

## ARGUMENT

### I. Liquidia infringes the storage limitations of claims 6 and 8 of the '066 Patent.

The district court erred twice in concluding that Liquidia does not infringe the '066 Patent's storage limitations. First, the court improperly based its non-infringement determination on UTC's purported failure to prove actual *past* infringement, rather than focusing on the scope of Liquidia's NDA. Second, the court inconsistently construed "storage" to

include storage that takes place during the shipment process but to exclude storage that takes place during the manufacturing process. Liquidia's response brief proposes new factual findings to justify the district court's decision.

### A. Liquidia's NDA allows it to infringe claims 6 and 8.

In the pre-launch Hatch-Waxman context, filing an ANDA or §505(b)(2) NDA is itself the infringing act, so infringement is evaluated based on what the applicant is asking FDA to approve without any separate inquiry into past or likely future infringement. *Sunovion*, 731 F.3d at 1278.

Liquidia seeks FDA approval to manufacture a treprostinil product through a process that includes storing isolated treprostinil salt without any temperature restrictions. Its NDA touts the stability of treprostinil sodium at ambient temperature for six months, relies on "representative" batches of Liquidia's bulk powder that were stored at ambient temperature during clinical trials, and incorporates Yonsung's Drug Master File (DMF), which contains no refrigerated-storage requirement. UTC Br. 62-63. That NDA alone makes Liquidia liable for infringement. *Sunovion*, 731 F.3d at 1280. And although no proof of past *actual*

infringement is required, Liquidia's history of storing treprostinil salt during shipment further confirms what its NDA shows—that the 2°-8°C storage range mentioned in some of Liquidia's documents is merely a recommendation and not the "requirement" that Liquidia suggests.

### 1. The record refutes Liquidia's argument that treprostinil sodium is "never" stored outside of a 2°-8°C range.

Liquidia argues that its NDA "requires" storage at 2°-8°C, and that treprostinil sodium is "never" stored outside that range. Liquidia Response Br. 48-51. These arguments are preposterous on this record. As UTC's principal brief described (UTC Br. 62-54), the NDA touted the stability of treprostinil sodium at ambient temperature and relied on clinical-trial data involving batches of bulk powder prepared from treprostinil salt stored at ambient temperature. The record showed actual use of treprostinil salt stored below 2°C. Liquidia accepted of batches of treprostinil salt stored above 8°C. And Liquidia's NDA identified batches that were not even monitored for storage temperature as "representative." Liquidia's response does not contest any of these facts. Unsurprisingly, given that undisputed record, the district court did not adopt the argument that the NDA "requires" storage between 2°-

8°C or that Liquidia "never" stores treprostinil sodium outside that range. To the contrary, the court acknowledged that Liquidia's NDA might "permit[]" Liquidia "to use TN exposed to ambient temperatures," Appx00032, and it acknowledged numerous batches Liquidia accepted where storage occurred at ambient temperature or where storage temperatures were not monitored, Appx00033-00035.

Nevertheless, the court held that UTC could not prevail because it did not demonstrate specific past instances in which batches shipped by Yonsung were stored at ambient temperature, accepted by Liquidia, and used in manufacturing Yutrepia for commercial sale. Appx00033-00035. And its sole basis for imposing this requirement was its citation to *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321 (Fed. Cir. 2010), a non-Hatch-Waxman case requiring proof of past "specific instances of direct infringement." Appx00032-33 (quoting *Fujitsu*). Yet *Sunovion* (which the district court brushed aside in a footnote) and numerous cases that followed it foreclose this rationale. *See, e.g.*, *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.,* 887 F.3d 1117, 1129 (Fed. Cir. 2018) ("[A] patentee does not need to prove an actual past instance of direct

infringement … to establish infringement" in a case involving an artificial act of infringement).

Liquidia barely defends the district court's reasoning and likewise gives *Sunovion* short shrift, briefly suggesting that the case is irrelevant because the NDA here "*requires*" 2-8°C storage and thus Liquidia's storage of treprostinil sodium "is outside" the scope of the patent. Liquidia Response Br. 52-53. But this distinction assumes the answer to the core disputed question: what the NDA permits. It also does not justify the district court's requirement, citing *Fujitsu*, that UTC prove "specific instances" of past infringement. That was the wrong legal standard, and the court's application of it warrants reversal.

### 2. Liquidia's reliance on the Raw Material Specification is misplaced.

Liquidia does not dispute that its NDA incorporates Yonsung's DMF, which touts stability at ambient temperature and includes no storage-temperature requirement (or storage-temperature-testing requirement) in its Specification. UTC Br. 62-63; *see also* Appx14534-14535 (Yonsung's Specification in DMF); Appx14874-14875 (Yonsung's Specification in Supply Agreement between LGM, Yonsung, and Liquidia). Nor does Liquidia dispute that even the most favorable

language for Liquidia in the DMF (in a snippet of a Yonsung label) merely uses the permissive "should" when referring to storage temperature. UTC Br. 62-63; Liquidia Response Br. 48; Appx14736. Instead, Liquidia asks this Court to ignore the DMF and rely on Liquidia's internal Raw Material Specification (RMS) and "an FDA site inspection" that examined storage temperature at Liquidia, without addressing any storage prior to or during shipment. Liquidia Response Br. 48. This argument is incorrect for several reasons.

First, the NDA is what matters under *Sunovion*, and the DMF is part of the NDA. Liquidia would prefer to ignore the DMF. It fails to address, much less rebut, UTC's reading of it. But this Court cannot disregard this piece of the NDA in evaluating infringement.

Second, Liquidia's own expert agreed that Yonsung's DMF contains the "controlling specification between Yonsung and Liquidia." Appx13122-13123(390:25-391:3). And it is certainly controlling as to *Yonsung's* storage conditions. *See* Appx14859 (Supply Agreement designating Yonsung's Specification as "[t]he specifications of the API"). Yonsung's Specification indisputably permits storage at ambient temperature—it includes no storage-temperature requirement,

Appx14534-14535, consistent with the DMF's representations (including stability data) that its treprostinil sodium is stable at ambient temperature for six months. Appx14738-14772. Thus, neither *Liquidia's* own internal RMS nor site inspections *at Liquidia* say anything about the infringing storage of treprostinil salt during shipment.

Third, while Liquidia does not dispute that Yonsung's DMF is expressly incorporated into the NDA, Liquidia provides no support for its assertion that its internal RMS is similarly incorporated. Liquidia *says* that the NDA "includes" the RMS, Liquidia Response Br. 48, but none of its three citations supports that assertion. The first, Appx07590, simply lists the phrase "Storage Conditions: 2°C to 8°C, protected from light and moisture" on the first page of the RMS. But it is the next page of the RMS that includes the test conditions that are actually *requirements*—the conditions that also appear in Yonsung's Specification—and those conditions conspicuously do not include (or test) storage temperature. *See* Appx07591 (RMS); Appx14534 (Yonsung's Specification); Appx13122(388:17-389:9) (RMS does not test for storage temperature).[1]

[1] Liquidia's reliance on 21 C.F.R. §211.80 is for this reason misplaced. That regulation requires compliance with "written procedures"

The second two, Appx12409 and Appx12411, are simply temperature records from Liquidia refrigerators. It is unclear why Liquidia cited these documents, but they do not support the propositions that Liquidia's internal RMS is incorporated into the NDA or that the NDA imposes a 2°-8°C storage requirement.

Finally, Liquidia's own witnesses contradicted any suggestion that the RMS imposes any enforceable temperature "requirement" above and beyond the controlling Yonsung DMF. Liquidia's corporate witness, Jeffrey Kindig, testified that the RMS was simply meant to effectuate a label snippet from Yonsung's DMF containing the permissive "should" language. Appx13103(311:12-23). And two other Liquidia witnesses testified that Liquidia can change its standard operating procedures, such as its internal procedures for receiving and handling treprostinil salt, without seeking FDA approval. Appx13080(224:14-17); Appx13082(231:19-25). Moreover, Liquidia decides on its own without FDA oversight whether to use for manufacturing treprostinil salt that

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containing "sufficient detail" about storage, handling, and sampling, among other procedures. But Liquidia offers no argument as to how the permissive language in the snippet of Yonsung's label or the "Storage Conditions" line on the first page of the RMS—which was not included in the RMS's list of *tested* requirements—could qualify.

was stored at ambient temperature. Appx13041(68:7-15); Appx13042(69:12-20). As this testimony demonstrates, the RMS establishes no new temperature requirements and certainly cannot be elevated above Yonsung's DMF.

### 3. The history of storage during shipment outside of the 2°-8°C range underscores why reversal is required under *Sunovion*.

If any question remained about whether the RMS or DMF imposes a "2°C to 8°C" storage *requirement*, the history of batches actually shipped from Yonsung confirms they do not. Liquidia spends pages of its brief maintaining that treprostinil sodium is "never" stored outside of the recommended 2°-8°C range, and that it has every incentive to treat that range as "a mandate, not an option," Liquidia Response Br. 31, 48-49, 55. But it completely contradicts those arguments when it finally addresses the extensive history of actual storage outside that range.

For example, Liquidia contends that refrigerated storage is *required*, and that Yonsung's compliance with that requirement is not only "establish[ed]" but "is, and will be, monitored with temperature loggers." *Id.* at 49. But when faced with indisputable evidence, acknowledged by the district court, that numerous batches were not

monitored for temperature during shipment at all, Liquidia's only response is to repeat the district court's assertion that this evidence does not prove past infringement by a preponderance of the evidence. *Id.* at 52. That mistaken focus on past infringement rather than the scope of the NDA misses the point—what on its face is merely a permissive recommendation (that storage "should" be within 2°-8°C) cannot be viewed as a requirement when it is not even consistently documented or subject to testing. As the regulation Liquidia cites makes clear, *requirements* are governed by "written procedures" described in "sufficient detail," 21 C.F.R. §211.80(a), and the DMF's recommended 2°C to 8°C storage range does not fit the bill.

Liquidia offers the same non sequitur in addressing evidence—again, acknowledged by the district court (Appx00034-00035)—that it knowingly accepted treprostinil sodium that had been stored at ambient temperature and released from shipment due to Yonsung's ambient-stability certification. Liquidia once again responds that this does not prove all the elements *past infringement*,[2] but the argument is no better

[2] Liquidia's contention (Response Br. 51-52) that these batches were "placed into quarantine" before this lawsuit is no escape hatch—Liquidia

the second time around. The history of Liquidia's acceptance of these shipments underscores that the 2°-8°C recommended range is just that—a recommendation.

When Liquidia finally gets to the evidence of its actual use of batches stored below the supposedly mandatory 2°C to 8°C range, Liquidia twists itself into a pretzel. Liquidia's sole justification is that "Yonsung has certified to the quality of TN stored below 2°C, which permits Liquidia to use it." Liquidia Response Br. 51 n.31. But Yonsung has also certified to the quality of treprostinil salt stored at ambient temperature. Appx14738-14772. Thus, Liquidia's argument is nothing short of an admission that the 2°C to 8°C range in the DMF and RMS is not a requirement and Liquidia's primary argument that treprostinil sodium is "never" stored outside this range is a farce.[3]

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conveniently omits that *all* shipments are placed into "quarantine" upon arrival. Appx13086-13087(248:21-250:4); 21 C.F.R. §211.82(b) (requiring quarantine upon arrival). It was only *after* Liquidia's corporate witness was deposed and pressed on those shipments that Liquidia decided not to use them for manufacturing—thus exemplifying the impossibility-of-compliance concerns this Court described in *Sunovion*. 731 F.3d at 1279; *see also* UTC Br. 64.

[3] Liquidia relies on three cases for the proposition that representations about an NDA's scope and an "NDA specification defining a proposed [product] in a manner that directly addresses the issue of infringement

This Court should reverse the district court's judgment of non-infringement of claims 6 and 8.

### B. The district court's erroneous and internally inconsistent construction of "storage" warrants reversal.

Rather than defend the district court's conclusion that "storage" cannot include treprostinil sodium left in the drybox during the extended PRINT manufacturing process, *see* Appx00036, Liquidia proffers findings about what occurred in the drybox. According to Liquidia, the court simply found that the treprostinil sodium was "active[ly] use[d]" in the drybox rather than stored there for three hours and concluded that "storage" cannot "encompass[] active process steps." Liquidia Response Br. 56. But the district court made no findings of this kind—Liquidia's reference to "active use" and "active process steps" can be found nowhere in the decision below. Its argument is also unsupported by evidence: as the district court acknowledged, UTC's expert testified that "TN is

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will control the infringement inquiry." Liquidia Response Br. 54 (citation omitted). Because, as discussed above, Liquidia's NDA *permits* ambient storage, these cases support UTC, not Liquidia.

'stored' in the drybox for three hours."[4] Appx00036. The court simply disagreed that this constituted "storage" for purposes of claims 6 and 8, because it occurs during the extended manufacturing process. *Id.*

The district court's construction is inconsistent with not only the plain and ordinary meaning of "storage" but also the court's construction of the same term in the shipping context where the court concluded that "material can be stored during shipment." Appx00033 n.9. Liquidia contends that *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282 (Fed. Cir. 2010), and *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317 (Fed. Cir. 2009), are "inapposite" because, according to Liquidia, the district court did not apply inconsistent constructions of "storage" here. Liquidia Response Br. 56. That argument just assumes the conclusion—that the district court *did* apply a consistent meaning of "storage." It did not: just as treprostinil sodium can be stored during shipment, so too can it be stored during the overall manufacturing process. Because the district court's

[4] Liquidia contends that UTC did not cite evidence showing that treprostinil sodium is stored for three hours in a drybox. Liquidia Response Br. 56 n.33. Not so. UTC cited the district court's opinion, which in turn pointed to UTC's expert testimony. *See* Appx00036 (citing Appx13049(99:24-100:7)).

non-infringement finding relied on this inconsistent construction of "storage," this Court should reverse.

## II. The ambient storage that occurs between steps 1-4 of Liquidia's PRINT process also infringes claim 8.

The district court further erred by erroneously construing when Liquidia begins preparing the "pharmaceutical composition" of claim 8 and when it begins preparing the "pharmaceutical product."[5] Liquidia tries to defend the district court's conclusion by offering a *new* construction, arguing that the "specification makes no distinction between a 'pharmaceutical composition' and a 'pharmaceutical product.'" Liquidia Response Br. 60. But the district court explicitly rejected this interpretation, "agree[ing] with UTC that a POSA would understand the 'pharmaceutical product' of claim 8 to be distinct from the 'pharmaceutical composition' of claim 6." Appx00037 n.12.

[5] Liquidia contends that "UTC admits that its problem with the court's decision is not its construction of the claims, but 'construction of when Liquidia begins preparing the 'pharmaceutical composition'[.]'" Liquidia Response Br. 57. This is an odd argument—"preparing a pharmaceutical product from the treprostinil salt after storage" *is* the relevant claim language, and whether the district court's construction of that language collapsed the distinction between "preparing a pharmaceutical composition" (claim 1) and "preparing a pharmaceutical product … after storage" (claim 8) is precisely what is at issue. Appx00132.

Liquidia also attempts to blur the line between the two distinct phases of the PRINT process by referring to it as a "single manufacturing process." Liquidia Response Br. 58. That Liquidia internally refers to the PRINT process as one manufacturing process does not mean that, for purposes of the claims, Liquidia begins preparing the pharmaceutical composition and the pharmaceutical product at the same time. Indeed, the PRINT process itself is delineated into two phases. During the first phase (steps 1-4), Liquidia prepares the pharmaceutical composition from the treprostinil salt. Appx14132. Between each step of this phase, Liquidia stores the substance for hours or even days at ambient temperature before proceeding to the next PRINT step. Appx29336-29346. Once phase one is complete, Liquidia ships the bulk powder to its contractor, Xcelience, to perform the second phase (steps 5-6). During phase two, Xcelience, not Liquidia, encapsulates the bulk powder into the final dosage form and packages this pharmaceutical product into commercial drug product kits for sale. Appx29346-29348, Appx00035-00036, Appx29336.

In between phases one and two (between steps 4 and 5), the bulk powder can be stored for not just hours or days but up to six months until

Liquidia ships it to Xcelience to prepare the pharmaceutical product. Appx29340, Appx29346-29348, Appx00035-00036, Appx29336. This six-month hold period plus the handover from Liquidia to Xcelience not only demarcate the two phases of the PRINT process but also demonstrate how Liquidia begins preparing the pharmaceutical composition in step 1 before ultimately having its contractor prepare the distinct pharmaceutical product in steps 5-6. *See* Appx29340-29341. And contrary to Liquidia's assertions, UTC's expert never agreed that "preparing a pharmaceutical product" begins at step 1. Liquidia Response Br. 57-58. UTC's expert was asked about the entire PRINT process, and Liquidia's brief misleadingly omitted the part of the question that UTC's expert was *actually* agreeing to:

> Q. And so I'm in the process now of making the pharmaceutical product; correct?
>
> **I'm in the print process once I put it into solution and start that process?**
>
> A. Correct. And during.

Appx13061(147:14-18) (omitted portion bolded). That omission is particularly misleading given that, immediately beforehand, UTC's expert expressly distinguished the two phases at issue: "[PRINT step 1

is] where *you're starting to make the pharmaceutical composition*, that bulk powder of LIQ 861 *before it's been packaged into the pharmaceutical product*." Appx13061(147:11-13) (emphases added).[6]

Liquidia next contends that if preparation of the pharmaceutical product does not begin until step 5, Liquidia still would not infringe because treprostinil sodium is not present "at all in any step" of the PRINT process once it "is dissolved in water at step 1." Liquidia Response Br. 59. This is yet another finding that the district court did not make.[7] And for good reason: Liquidia's argument is belied by its own

[6] Liquidia also cites its own expert's testimony. Liquidia Response Br. 57. But he simply offered the conclusory assertion that *he* "consider[s] these [PRINT steps 1-4] to be steps involved in preparing the pharmaceutical product." Appx13137(450:12-15). He offered no analysis of the composition/product distinction.

[7] Liquidia also briefly contends that the "hold times" between PRINT process steps could not be storage because the material is "drying" while it is being stored—purportedly "an active process." Liquidia Response Br. 59. But as with Liquidia's "active use" argument regarding the drybox, this is yet another finding the district court did not make. Instead, the court relied on an erroneous construction of the claim term "preparing a pharmaceutical product from the treprostinil salt after storage." Likewise, Liquidia argues that "none of the hold times for Steps 1-3 indicate storage at ambient temperature." *Id.* The district court did not make this finding either, and Liquidia ignores how its own NDA provides for "[b]ulk LIQ861 inhalation powder manufacturing activities [to be] conducted … under controlled temperature … conditions (18°C to 24°C …) *unless otherwise specified*." Appx29336 (emphasis added). The

labeling, which states that "YUTREPIA contains treprostinil sodium." Appx15622. It also displays the structural and molecular formulas of treprostinil sodium and explains that each Yutrepia capsule "contains white to off-white powder of treprostinil sodium."[8] Appx15623.

Liquidia's process and labeling thus confirm that Liquidia begins preparing the pharmaceutical composition at PRINT step 1 but that its contractor only begins preparing the pharmaceutical product at PRINT step 5. Appx29336, Appx29346-29348. The holding times between PRINT steps 1-4 when Liquidia stores the composition, which contains treprostinil sodium, at room temperature thus constitute ambient temperature storage under claim 8 and require reversal. Appx13065-13066(162:19-165:17).

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hold times for steps 1-3 do not specify any other temperature, meaning that they are conducted at the default (ambient) temperature of 18°C to 24°C. Appx29336-29339; Appx13050(101:16-102:6, 102:19-103:6); Appx 13065-13066(162:19-165:17). Moreover, Liquidia's own corporate representative agreed that the NDA allows storage at room temperature after Steps 1-3. Appx13040(61:4-63:5).

[8] Liquidia mischaracterizes UTC's reference (UTC Br. 86) to "treprostinil salt and a final treprostinil product." Liquidia Response Br. 59 n.35. At no point did UTC state that Yutrepia does not contain treprostinil salt. And UTC's reference to a "final treprostinil product" was just that—a reference to a final product containing treprostinil.

## III. Liquidia fails to address the legal errors in the district court's anticipation analysis.

The district court misconstrued the product-by-process claims as directed to the treprostinil compound rather than to a "pharmaceutical composition" with relevant impurities, and it erroneously placed the burden on UTC to *dis*prove that the product disclosed in Moriarty 2004 is the same as the claimed composition. UTC Br. 77-84. Had the district court applied the correct construction and burden, it could not have determined that Liquidia established anticipation by clear and convincing evidence. Liquidia's brief merely repeats, rather than addresses, the district court's errors, and obfuscates the facts relevant to anticipation.

### A. Liquidia, like the district court, misconstrues the scope of the claimed "pharmaceutical composition" by ignoring its impurities.

Claims 1-3 and 6 claim a "pharmaceutical composition" that is prepared by taking a "starting batch of treprostinil" containing impurities generated through prior alkylation and hydrolysis steps and reducing the levels of those impurities through salt formation. The claimed product of these product-by-process claims is not the treprostinil compound alone, but the resulting "composition" *including* reduced levels

of specific impurities not achieved through existing purification processes.[9] UTC Br. 77-82; *cf. Digitech Image Techs. v. Elecs. for Imaging, Inc.*, 758 F.3d 1344, 1349 (Fed. Cir. 2014) (noting that "a composition of matter requires the combination of two or more substances"); Appx13159(536:7-11). For example, evidence at trial demonstrated that crystallization during salt formation isolates treprostinil from stereoisomers like 15-epi-treprostinil (3AU90) in ways that traditional purification methods like column chromatography could not. *Id.* at 84-85. The '066 Patent distinguishes the claimed treprostinil composition, which has levels of particular impurities reduced through salt formation, from prior-art treprostinil products manufactured through other processes. This is consistent with how the PTO twice interpreted the plain language of the claims, thus affording the granted patent a presumption of structural novelty over Moriarty 2004.[10]

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[9] That neither party sought construction of "pharmaceutical composition" during *Markman* proceedings is irrelevant. Liquidia did not make clear until trial that it was relying on the Moriarty 2004 publication for anticipation. *See* Appx09333-09340.

[10] The PTO allowed the '066 Patent claims because they are directed to a "pharmaceutical composition" with express impurities-related limitations, unlike the '393 Patent claims, which were directed solely to the treprostinil "compound." UTC Br. 80-81. And the PTAB later

Liquidia's primary objection to this plain reading of the claims is that they do not recite any specific impurities and treprostinil is the only component of the "pharmaceutical composition" recited in the preamble. Liquidia Response Br. 34. But nothing in product-by-process case law requires that all structural components of the claimed product be explicitly recited in the preamble or elsewhere in the claim. Rather, this Court has made clear that "a new product may be patented by reciting source or process limitations so long as the product is new and unobvious." *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1366 (2009). That is the very purpose of a product-by-process claim, which is why Liquidia's criticism of UTC for "tout[ing] the alleged process benefits" is so absurd. Liquidia Response Br. 36. When an inventor defines a new product by its source or manufacturing process, the

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declined to review the '066 Patent because the asserted prior art, including Moriarty 2004, failed to meet the "claim 1 require[ment]" regarding impurities. *Id.* While Liquidia references the '393 IPR (Br. 36, 43 n.26) as support for anticipation here, the district court held that the '393 Patent is not prior art and its "product" is "irrelevant" to the validity of the '066 claims. Appx10871. And whatever other issues the PTAB discussed concerning the '393 Patent, it did not disagree that 3AU90 (an impurity from alkylation and hydrolysis steps) was higher in prior processes that did not use salt purification. *SteadyMed Ltd. v. United Therapeutics Corp.*, IPR2016-00006, 2017 WL 1215714, at *15 (PTAB Mar. 31, 2017).

"structural and functional differences" that result from the new process are relevant to the anticipation inquiry even when those structural differences are "not explicitly part of the claim." 580 F.3d at 1370.[11]

Liquidia's contrary view would require inventors to expressly recite all structural aspects of a claimed product that are material to patentability. That would undermine the traditional role of product-by-process claims in allowing inventors to define a product using process steps when the structural features of the product were "difficult or impossible" to fully analyze and describe. *Abbott Labs. v. Sandoz Inc.*, 566 F.3d 1282, 1294 (Fed. Cir. 2009) (en banc). Recognizing this need, this Court has instructed that product-by-process claims "will issue subject to the ordinary requirements of patentability," *id.*, including the ordinary "presumption of patent validity" enjoyed by patentees, *Amgen*, 580 F.3d at 1367. Liquidia effectively asks this Court to overturn this well-established precedent.

Liquidia would also have courts disregard intrinsic evidence demonstrating the structure conferred by the process limitations,

[11] The district court made the same error—faulting the inventors for failing to expressly recite a specific "purity percentage" or "impurity profile." Appx00041.

notwithstanding this Court's contrary precedent. UTC Br. 81-82; *see also Amgen*, 580 F.3d at 1367 (citing the prosecution history and specification for the structure imparted by process limitations).[12] Here, that includes PTO's determination that, in light of the impurities-reduction limitations, the claims of the '066 Patent are directed to a novel "composition" that is distinct from "the product of Moriarty." Appx03818; Appx03825. This is consistent with the specification. *See, e.g.*, Appx00132(17:29-32) ("impurities carried over from intermediate (i.e. alkylation of triol and hydrolysis of benzindene nitrile)" are removed during salt formation); Appx00046. Further, as the district court found, a POSA reading the '066 specification would have understood that the alkylation and hydrolysis steps used to make treprostinil change the color of the reacting substance to brown and then yellow, but the claimed "salt formation step results in an off-white material, *indicating the generation and lowering of impurities from the alkylation and hydrolysis*

[12] Liquidia's only response to these authorities is the question-begging assertion that the impurities-lowering limitation confers no structure. 40 & n.24. Liquidia argues that "*Nordt* is inapplicable here" but does not deny that "the structural nature of [limitations] can be gleaned from the plain claim language." *In re Nordt Dev. Co.* 881 F.3d 1371, 1376 (Fed. Cir. 2018) (collecting cases).

*steps*." Appx00045-00046 (emphasis added). Under Liquidia's theory, the structural change indicated by this color change is irrelevant simply because the claims do not name the specific impurities.

The inventors were not required to recite each of the specific impurities for them to be relevant to the anticipation analysis. Rather, as is typical for product-by-process claims, the inventors were entitled to define the claimed composition by identifying the alkylation, hydrolysis, and salt-formation steps that imparted the resulting composition with uniquely low levels of specific impurities. Further, the express impurity-reduction limitations are precisely what demonstrate the claimed composition's structural features. As Liquidia's expert Dr. Winkler explained, a POSA would consider the impurities-related claim language as limitations "describing the product." Appx13126(406:3-5).[13]

In light of the scope of the claimed product, Liquidia should have been required to establish by clear and convincing evidence that Moriarty

[13] Liquidia gerrymanders its criticism around Winkler's testimony, arguing that "[n]o *UTC* witness supported UTC's position that this language is a 'product' limitation as opposed to a process step." Liquidia Response Br. 34 (emphasis added). UTC had no burden to put on additional evidence of this undisputed point established by Liquidia's own expert.

2004 disclosed the full scope of the same treprostinil composition with the reduced levels of hydrolysis and alkylation impurities achieved by the salt-formation process of the recited claims. *See Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) ("[D]ifferences between the prior art reference and a claimed invention, however slight, invoke the question of obviousness, not anticipation."). But because the district court misconstrued the "pharmaceutical composition"—ignoring the structure conferred by the claimed process steps—it failed to impose that burden on Liquidia, which offered no evidence of that disclosure. Instead, the court erroneously rested its anticipation analysis on the chemical structure of the treprostinil compound and its purported overall purity percentage—which are not the distinguishing features of the product claimed by the patent and therefore cannot demonstrate anticipation.

### B. Liquidia's effort to shift the burden to UTC is contrary to precedent.

To defend the district court's anticipation conclusion, Liquidia attempts to shift the burden to UTC, repeatedly faulting UTC for "fail[ing] to show" that the product of Moriarty 2004 is different from the claimed pharmaceutical composition. Liquidia Response Br. 32-33;

*accord id.* at 41-42. But this Court has made clear "[o]n numerous occasions" that the burden of proving anticipation begins and remains with the patent challenger. *Lisle Corp. v. A.J. Mfg. Co.*, 398 F.3d 1306, 1316 (Fed. Cir. 2005); *see also TP Lab'ys, Inc. v. Pro. Positioners, Inc.*, 724 F.2d 965, 971 (Fed. Cir. 1984). This is no less true for the structural features of product-by-process claims than for other claims. *See Amgen*, 580 F.3d at 1370 ("to prove invalidity, [the patent challenger] had to show that recombinant EPO was the same as urinary EPO, even though urinary EPO was not made recombinantly" and "did not meet its burden").

Liquidia cites *Greenliant Systems, Inc. v. Xicor LLC*, 692 F.3d 1261 (Fed. Cir. 2012), as supposedly imposing a burden on "the patentee" in a product-by-process case. Not so. *Greenliant* discusses the standard for establishing patentability during prosecution—which UTC has already met—not the standard for proving anticipation in post-grant district court litigation. 692 F.3d at 1268. In *this* context, the '066 Patent is entitled a presumption of structural novelty over Moriarty 2004, and *Amgen* is unequivocal and dispositive in placing the burden on Liquidia to prove anticipation. If anything, Liquidia's "burden is especially

difficult" because it "attempts to rely on prior art that was before the patent examiner during prosecution." *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed. Cir. 2004) (quotation marks omitted).

If the district court had properly construed the claim limitations, it could not have found that Liquidia met its burden by clear and convincing evidence. There is no dispute that the text of Moriarty 2004 discloses nothing about the levels or sources of specific impurities in the treprostinil product it describes. Nor did Liquidia advance a theory that the process disclosed in Moriarty *inherently* resulted in a composition with the same levels of relevant impurities as the claimed process. Liquidia's expert did not perform any testing to determine what impurities would have been present in the sample disclosed in Moriarty 2004, Appx13157-13158(529:21-530:24, 531:7-16), so as to demonstrate "that the process limitations [described in the product-by-process claims] do not result in an invention distinguishable from the prior art." *Cubist Pharms., Inc. v. Hospira, Inc.,* 75 F. Supp. 3d 641, 668 (D. Del. 2014), *aff'd,* 805 F.3d 1112 (Fed. Cir. 2015). Liquidia also expressly waived any inherency argument. Appx31039. And while Liquidia spends much real estate arguing about evidence relating to a product manufactured by

UTC through its prior "Chicago process," this is an argument for invalidity under the on-sale bar, which Liquidia also expressly waived. Appx31039. The only anticipation theory Liquidia offered at trial was anticipation through the express disclosures of a printed publication. And yet, Liquidia offered no evidence that Moriarty 2004 *disclosed* the claimed treprostinil "composition" with reduced levels of alkylation and hydrolysis impurities. Thus, there is no way Liquidia could have proven that the sole asserted prior-art reference introduced at trial, Moriarty 2004, anticipated the asserted claims.

At the same time, even though UTC bore no burden to show novelty, Liquidia is wrong in contending that UTC presented no evidence on the issue. As described at length in UTC's principal brief (at 84-87), Dr. Toste explained how the salt-formation process removes specific impurities, and Dr. Walsh presented data comparing relevant impurity levels in batches of treprostinil manufactured with and without salt formation. Liquidia has no persuasive answer to Dr. Toste's evidence, so it complains that the evidence was given in the context of infringement. But relevant evidence introduced at trial is evidence for any issues in the case, especially when it pertains to the proper construction of claims, which

"are construed the same way for both invalidity and infringement." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1330 (Fed. Cir. 2003). Indeed, Liquidia itself relies on infringement testimony to argue anticipation. *See, e.g.*, Liquidia Response Br. 34 (citing Toste and Nuckolls).

Liquidia also criticizes Dr. Toste for "focus[ing] on the alleged advantages of the claimed ***process*** of salt formation compared to prior chromatography purification processes." Liquidia Response Br. 42 (emphasis Liquidia's); *see also id.* at 34 (similar criticism of Toste and Nuckolls). Far from undermining Dr. Toste's testimony, Liquidia's argument neatly encapsulates why his testimony is relevant: the structural changes from the salt-formation *process* are what make these product-by-process claims patentable. That is how product-by-process patents work.

Liquidia also fails to provide any reasoned explanation for why the district court could disregard Dr. Walsh's data simply because it compared batches of treprostinil salt to batches of treprostinil free acid. Dr. Walsh compared the levels of specific *impurities* following salt-formation purification (recited in the '066 Patent) against the levels of

specific *impurities* following earlier purification processes—an apples-to-apples comparison. The district court had (just 19 pages earlier) found that the relevant impurities levels are fixed after salt formation; later processing steps, even Liquidia's extensive PRINT processing steps, "do[] not affect those impurities." Appx00025. Yet, it disregarded Dr. Walsh's comparison because Dr. Walsh did not put the treprostinil salt through post-salt-formation processing steps (acidification to regenerate a free acid). Liquidia has no answer to this inconsistent analysis—it provides no basis in evidence, science, or logic to suggest that the levels of impurities from "*prior* alkylation and hydrolysis" steps would change if the same batches of treprostinil salt were simply reconverted to free acid. Instead, Liquidia pivots to talking about *other* evidence. Liquidia Response Br. 43-44.

Moreover, Dr. Winkler relied on data that assumed treprostinil salt and free acid are comparable, making the district court's rejection of Dr. Walsh's testimony all the more erroneous. UTC Br. 86; Appx13143(473:16-22).[14] Liquidia does not meaningfully dispute this

[14] It was based on this compilation of treprostinil salt and free acid data from the '393 IPR that the district court concluded "[t]he average

and instead argues waiver—but UTC could not have waived a record fact that was not relevant until the district court discounted Dr. Walsh's evidence while simultaneously crediting Dr. Winkler's.[15]

### C. Liquidia's remaining evidence does not address the district court's legal errors.

The remaining evidence Liquidia raises fails to address the deficiencies in the district court's reasoning. Both Liquidia and the district court relied on UTC's confidential FDA submissions concerning its "Chicago" and "Silver Spring Process[es]," but that evidence cannot satisfy Liquidia's burden of establishing anticipation.

First, these confidential regulatory submissions were not prior art. *See Nobel Biocare Servs. AG v. Instradent USA, Inc.*, 903 F.3d 1365, 1375 (Fed. Cir. 2018). Nor could their contents inform the prior art under any theory asserted at trial. As noted above, Liquidia expressly waived, and continues to disclaim, any reliance on commercial products made using the Chicago process as prior art under the on-sale bar. Appx31039.

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purity of UTC's batches of UT-15 treprostinil made by … the '066 process" is "99.7%." Appx00039; Appx00043.

[15] Liquidia does not even feign prejudice. As Liquidia knows, Dr. Winkler was also an expert in the '393 IPR and was aware that the data he relied on contained both salt and free-acid forms.

Likewise, Liquidia waived reliance on the inherency doctrine to establish properties or results of Moriarty 2004 that were not expressly disclosed in the printed publication itself. Appx31039. Thus, the only anticipation theory before the district court was anticipation by the express disclosures of Moriarty 2004.

But the district court made no finding that Moriarty 2004 *disclosed* the product of the Chicago process with its associated impurities levels. Nor could it. Liquidia presented no evidence that the level of *any* impurity was *disclosed* in Moriarty 2004. Instead, the district court and Liquidia filled in disclosures missing from the publication with later-discovered confidential data about UTC's commercial process. This it could not do. Anticipation "requires that all aspects of the claimed invention were already described in a single reference," which cannot happen "if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576-77 (Fed. Cir. 1991); *see also Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1383 (Fed. Cir. 2018) ("the incomplete description of the composition elements [in the printed publication] denied skilled artisans

from having access to that composition").[16] The district court's reliance on the Chicago process data also ignored differences between that process and the Moriarty 2004 that are plain from a comparison of the printed publication with the "former" Chicago process described in the '066 patent specification.[17]

But even setting aside these problems with Liquidia's reliance on UTC's regulatory submissions, the comparisons between the Chicago and Silver Spring processes still cannot support anticipation. Regulatory statements to FDA that the products of the two processes are of "equivalent quality" or of "very similar impurity profile and similar acceptable criteria" do not establish that the product of one process in fact possesses the same levels of specific impurities as the other, as

[16] This gap-filling was particularly problematic in light of the multiple prior-art methods for synthesizing treprostinil. Appx13155(522:10-523:3) (Liquidia's expert testifying regarding the known synthesis routes as of 2007).

[17] UTC's Chicago (or "Former") Process was first disclosed in the patent specification, which reports, *inter alia*, different batch size, yield, and purity than Moriarty 2004. Appx00132, 17:25. *Compare, e.g.*, Appx29418 (Moriarty 2004) (batch size 441g, 83% yield, 99.7% purity), *with* Appx00132 ('066) at 17, Steps 51-53 (reporting "Former Process" batch size 535g, 91% yield, and "~99.0%" Purity). *See also,* Appx30977-Appx30979 (citing Appx31011-31013 at ¶¶97-103) (collecting evidence of process differences).

required to prove anticipation here. The purity specifications in the documents reflect minimum regulatory thresholds negotiated with FDA to ensure safety and efficacy, not actual analytical testing results. "The test for anticipation … is not whether two substantially similar (but not necessarily identical) structures can be used for the same purpose and in compliance with some standard." *Belcher Pharms., LLC v. Hospira, Inc.*, 450 F. Supp. 3d 512, 543 (D. Del. 2020), *aff'd,* 11 F.4th 1345 (Fed. Cir. 2021). Instead, the question is "whether the prior art references anticipate the structure that would result from the claimed process." *Id.* Liquidia did not prove anticipation under that test.

## CONCLUSION

This Court should reverse the district court's conclusions that UTC did not prove infringement of claims 6 and 8 of the '066 Patent and that claims 1, 2, 3, and 6 of the '066 Patent are invalid as anticipated.

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Respectfully submitted.

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## CERTIFICATE OF SERVICE

I, Jaime A. Santos, hereby certify that on February 13, 2023, I electronically transmitted the foregoing document to the Clerk's Office using the CM/ECF System. I certify that all participants in this case are registered CM/ECF users and that service will be accomplished by the CM/ECF system.

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## CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Circuit Rule 28.1(b)(3)(A). This brief contains 6,999 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b)(2).

This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate Procedure 32(a)(6). This brief has been prepared in a proportionally spaced typeface, 14-point Century Schoolbook font, using Microsoft Word for Office 365. As permitted by Fed. R. App. P. 32(g), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

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